PSJ2 Exh 44

OXYMORPHONE LEARNING SYSTEM

Module 3

OPANA™ Risk Management Program

For Sales Training Background Purposes Only

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IV. EVALUATION PLAN

Introduction

The abuse, misuse, and diversion of opioids and the resulting adverse events are serious problems. Without action on the part of pharmaceutical companies that market opioids, these problems could lead to further governmental restrictions on opioids that could interfere with effective pain management.

The Risk Minimization Action Plan (RiskMAP) for OPANA™ (called EN3202/03 in the text) is a program developed by Endo that "aims to promote the safe and responsible use of the product while concurrently minimizing abuse, misuse, diversion, and other adverse events through appropriate drug labeling, tight controls on distribution, proactive pharmacovigilance, extensive education of healthcare professionals and sales personnel, and funding of clinically meaningful research."

In this module, most of the text of the RiskMAP is reproduced. It will appear in a different font throughout the module, interspersed with commentary explaining the content and adding details where needed.

The details of the plan include training of sales representatives in the proper marketing of opioids. Some of the problems with OxyContin® were caused by improper selling techniques. You must also understand the details of the plan in order to communicate them to the healthcare professionals who are crucial to the plan's effectiveness.

Glossary

Addiction: primary, chronic neurobiologic disease characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Tolerance: state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more drug effects over time.

I. Overview of the Need for Risk Management with Opioids

Undertreatment of pain produces economic and social costs over tens of billions of dollars each year in the U.S. *[AAPM, 1997, 1]* Opioids have been proven to treat chronic pain effectively and thus can help eliminate undertreatment, if used properly. However, abuse, misuse, diversion, fears of addiction, respiratory depression, and tolerance all work against the proper use of opioids.

In this section, we will discuss the benefits that a proper risk management plan can provide and the risks that need to be overcome. We will then summarize the goals of a risk management plan and the pieces that need to be included to make it successful.

Learning Objectives

1. State the benefits of opioids in pain management.
2. Identify the risks associated with opioids.
3. Identify the goals of a successful risk management program.

Key Concepts

1. Opioids have been proven to increase functioning and quality of life in patients with chronic pain. Proper pain treatment can reduce its enormous economic, social, and personal costs.
2. The risks of opioid use include abuse and misuse, addiction, side effects such as respiratory depression, and diversion.
3. The goals of risk management are proper product labeling, effective monitoring and surveillance, and education of physicians and patients in the use and risks of opioids. If these goals are met, a risk management plan can minimize those risks and optimize pain treatment.

A. Benefits of Pain Management with Opioids

In clinical studies, opioids have been proven to be effective for managing chronic pain. They increase functioning and quality of life and prevent needless suffering. Professional pain organizations recognize their crucial role in pain management and have published consensus statements outlining plans for using opioids while avoiding the risks associated with them.

1. Studies of Increased Functioning and Quality of Life.

> Intractable chronic pain drains its victims of quality of life and the United States (US) economy of billions of dollars in healthcare costs and lost productivity. Multiple studies have confirmed the usefulness of opioids in the treatment of chronic pain and cite the relatively low incidence of abuse and addiction among most patients who receive opioid analgesics. The literature further suggests that the potential for increased functioning and improved quality of life significantly outweigh the risk of abuse (American Academy of Pain Medicine, 1997).

Many studies confirm the efficacy of long-acting opioids in chronic pain. A review of 10 studies of controlled-release morphine in patients with chronic cancer pain found a decrease in mean pain scores to just 2.2 on a 10-point scale. The reviewers also found that quality of life was also improved. In another study of patients with chronic noncancer pain, 79 of 100 patients reported good or partial pain relief. A significant correlation between pain relief and increase in performance was also noted. *[Vallerand, 2003, 438]*

2. Position Statements from Professional Organizations.

> Professional organizations, such as the American Pain Society (APS) and American Academy of Pain Management, recognize the benefits of adequate pain management and the pivotal palliative role for opioids in the treatment of chronic non-cancer pain, as well as moderate-to-severe acute pain (American Academy of Pain Medicine, 1997).

The American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) published a consensus statement in 1997 about the use of opioids for the treatment of chronic pain. Two developments led these organizations to produce the statement. The first was increasing recognition in the 1990s that effective pain management

can improve functioning and quality of life and thus substantially reduce the economic and social costs of pain. The second was that state governments were beginning to pass laws regulating the chronic use of opioids. The goal of the statement was to urge governments not to interfere with the proper use of opioids but rather to focus their policies on issues that lead to drug abuse and diversion. *[AAPM, 1997, 1]*

To achieve this goal, the consensus statement first described the problems inherent in opioid therapy, then set out a list of principles for good professional practice. These principles were designed to address and minimize the problems with opioids.

The problems with opioid treatment, according to the statement, include **addiction**, respiratory depression and other side effects, **tolerance**, diversion, and fear of regulatory action on the part of healthcare professionals. *[AAPM, 1997, 1]* Each of these problems is then explained and proven means of handling them are stated.

The statement then goes on to say that publishing practice guidelines lets regulators distinguish accepted medical practice from unaccepted practice and thus concentrate their efforts appropriately. *[AAPM, 1997, 2]*

Finally, the statement provides a basic model for using opioids properly. It starts with complete evaluation of the patient and the development of a treatment plan. If the treatment plan includes opioids, the patient should be fully informed of the risks and then a trial of opioid efficacy performed. In complex cases, a pain specialist or psychologist can help in deciding whether opioids are necessary. Once a patient is prescribed an opioid, periodic reassessment is imperative to ensure that the drug is still effective and to determine whether it is still needed. Finally, the entire process should be documented properly. *[AAPM, 1997, 3]*

This statement is the basis for risk management programs that are developed for opioids. These programs focus on education of both

physicians and patients so that everyone involved knows the concerns and can make intelligent choices. They also focus on oversight and proper documentation so that any problems that arise are identified and dealt with promptly. As you read Sections B–D, make note of these guidelines to remind yourself why each piece of the risk management program is in place.

B. Risks Associated with Opioid Analgesics

Two risks peculiar to opioids and other controlled drugs are abuse/misuse, and addiction. Understanding these risks and developing guidelines for minimizing them is crucial to risk management.

1. Abuse and Misuse.

Unfortunately, prescription opioid analgesics, like all medications, are associated with a number of risks. Chief among these are the risks of abuse, misuse, and addiction. According to the 2004 National Household Survey on Drug Use and Health, people who had used pain relievers' non-medically at least once during their lifetime increased 7% from 2002 to 2004, for a total of 31.8 million Americans (Gfroerer, 2003). The reported rise of prescription drug abuse is corroborated by data on the consequences of such use. According to Substance Abuse and Mental Health Services Administration's (SAMHSA's) Drug Abuse Warning Network (DAWN), emergency department contacts for non-medical use of substances for psychic effects, overdose, dependence, or suicide attempts increased from 69,011 in 1999 to 119,185 in 2002 for narcotic analgesics. The Treatment Episode Data Set (TEDS), also administered by SAMHSA, collects data on admissions to federally funded drug and alcohol addiction treatment programs noted that between 1999 and 2003, treatment admissions for opiate drug addiction treatment (exclusive of heroin) increased from 1,382 admissions in 1999 to 9,171 in 2003.

Importantly, nearly half of the prescription drug abuse has been observed in youth and young adults (aged 12 to 25) (Gfroerer, 2003). Use of these drugs by young people has dramatically increased for all categories of pharmaceuticals, most prominently pain relievers (nearly 2 million in 2000), followed by tranquilizers (nearly 1 million) (Gfroerer, 2003).

The number of people in the U.S. who abuse opioids and other pain relievers is greater than that for any drug except marijuana. In 2002, almost 2 million people were believed to abuse pain relievers. The

numbers tell us that this is not a small problem. Many of these people were abusing OxyContin®, a long-acting opioid that was introduced in 1995.

Why do patients abuse opioids? Patients report increased energy, feelings of euphoria and invincibility, and the feeling that they can do anything. *[Hays, 2004, 4–5]*

Misuse and diversion are also serious problems. A single, 40-mg OxyContin tablet sold for $40 in 2001. As a result, there were many pharmacy robberies in which the drug was specifically targeted. *[Hays, 2004, 2–3]* Fake and altered prescriptions, patients selling their prescriptions, and patients going to several doctors to get prescriptions were other mechanisms of diversion.

2. Patient Types. Studies have shown that one of the best ways to limit abuse and misuse is to choose appropriate patients for opioid therapy. A screening tool called the Screener and Opioid Assessment for Patients with Pain (SOAPP) was developed by experts to help physicians select such patients. This group developed a list of behavioral and psychological characteristics that predict possible opioid abuse. The most important of these characteristics were antisocial behavior history, substance abuse history, medication-related behaviors (eg, improperly using medications), and doctor-patient relationships. Patients with poor scores in these areas would be more likely to abuse opioids than other patients. From these behaviors, a list of 24 items was developed for patients to answer on a five-point scale with 0 = "Never" and 4 = "Very often." Items include statements such as the following. *[Butler, 2004, 69–70]*

- How often do you do things that you later regret?
- How often have you felt a craving for a medication?
- How often have others suggested you have a drug or alcohol problem?

- How often, in your lifetime, have you had legal problems or been arrested?

Patients can take this test when they are in the waiting room of the doctor's office, or they can take it home with them. The scores can help physicians decide who is a good candidate for opioid therapy and who should be treated by other methods. Patients who fall in the middle might be treated in a more structured way to help them avoid abusing the drug.

3. Addiction. Addiction is a compulsive disorder in which the patient becomes preoccupied with obtaining and using a drug, even though it is ruining his/her life. Studies show, however, that patients who require an opioid for pain relief have a low frequency of developing an addiction to the drug. *[AAPM, 1997, 2]*

Again, proper choice of patient can minimize the likelihood of developing addiction. A patient who truly needs the drug, and is educated about the risks and benefits of opioids, will likely not become addicted.

C. Goals of a Risk Management Program

The most recent extensive public discussion of opioid risk management programs took place in September, 2003, at the meeting of the Anesthetic and Life Support Drugs Advisory Committee of the US Food and Drug Administration (FDA). The key messages of that meeting with regard to risk management were:

- The product label should include recommendations for routine assessment of addiction risk and outcomes, although tools to assist physicians in this task were lacking
- Improved monitoring and surveillance of patients on opioid therapy was needed
- Education on opioid prescribing and abuse risks must be made widely available to clinicians
- The major limitations of existing surveillance systems were:

  - No information on pathways to prescription opioid abuse
  - No information on the risk of addiction among patients with chronic pain

- Pharmaceutical companies on their own should not determine when a pattern of opioid prescribing or patient behavior should be viewed as inappropriate.

The goals and objectives for this RiskMAP are to minimize the following liabilities with opioid class of drugs as it pertains to EN3202/03.

- Aberrant behavior such as drug abuse, misuse, and addiction
  - Among patients
  - In the community, particularly among young adults
- Unintentional drug overdose
- Accidental exposure
- Diversion from distribution/manufacturing facilities
- Improper patient selection
- Fraudulent prescription activity
- Inadequate patient education

A substantial initiative is to facilitate all of the above goals with improved approaches to surveillance.

An effective risk management program is designed to allow patients to benefit from the efficacy of opioids while avoiding the problems of abuse, misuse, diversion, and addiction. The primary methods for achieving these ends are effective product labeling, close monitoring and surveillance of the medication's use, and educating physicians on how to minimize the problems.

1. Product Labeling. Proper product labeling can go a long way in educating both physicians and patients about opioids and the risks associated with them. A package insert (PI) describes all of the following:

- appropriate product dosing (starting dose, dosage increases)
- how to take the product properly (e.g., swallowing a capsule instead of chewing it)

- things a patient should not do when taking the product (eg, combine an opioid with alcohol)
- common and/or serious side effects (e.g., respiratory depression) and how to deal with them if they arise

The PI, however, is a legal and scientifically complex document that many patients may not understand. Additional pieces can use less scientific language to convey all of the above information to patients. Better-informed patients make wiser decisions about their treatment and are less likely to make mistakes that can lead to trouble.

2. Monitoring and Surveillance.

The first step in addressing any public health problem is appropriate surveillance; yet, existing surveillance systems for prescription opioid abuse, including those cited above, have been widely acknowledged as inadequate (Arfken, 2003; GAO, 2003). At this point in time, real-time product-specific surveillance does not exist. Existing databases either provide data several years after the fact (e.g. National Survey of Drug Use and Health), or do not discriminate with any known degree of accuracy between abuse rates of specific products (e.g. key informant networks). Discussions about risk management mean little without up-to-date product specific information; Endo has recognized and begun to address this need.

Postmarketing surveillance provides real-world data that can be used to determine if a drug is being abused or misused at a higher than expected rate and the types of problems that are resulting. One problem with many databases is that the data are out of date.

Several general surveillance systems exist to collect such data and make it available to oversight committees and governmental agencies. These systems collect data from hospital records on substance abuse cases, reports of serious adverse events from hospitals or physicians, poison control centers reporting overdoses, admissions to substance abuse centers, police and federal criminal records, and large community-based surveys of drug use. *[Arfken, 2003, S98–S99]* Tracking data on prescription writing and filling can show inconsistencies that can be followed up.

The most important part of surveillance and monitoring is to use multiple methods. A single method may miss geographic regions and certain target populations and may not be varied enough to detect some patterns of abuse. *[Arfken, 2003, S104]* For example, the SOAPP questionnaire can detect some patients who are not good candidates for opioid therapy, but patients can lie about their history. Combining the questionnaire with urine screening before and during treatment to determine if the patient had illicit or nonprescribed drugs in his/her system has been shown to identify more patients with inappropriate drug-taking behavior than either method alone. *[Katz, 2003, 1097]*

Of course, there must be oversight committees whose job is to take all the available data and analyze it. Without such groups, the best surveillance methods are useless.

3. Physician Education. One final part of an effective risk management plan is proper physician education. Many physicians are not adequately trained in pain management and the use of opioids. This is a crucial gap in risk management of opioids that must be filled. Physician education through a well-written PI, published guidelines for the proper use of opioids, and proper patient selection is imperative for risk management to work.

Continuing education from experts in the pain management field on certain topics can also improve the physician's ability to assess a patient's likelihood of abusing a prescribed opioid. For example, giving a physician a detailed review of how the SOAPP questionnaire items were selected and what each one is designed to assess could make the use of that form much more effective. Physicians can also become acquainted with local groups who provide structures that encourage patients at risk of abuse to adhere to their treatment plan.

In general, physicians are the front lines in the battle against abuse and misuse of opioids. The better informed they are, the better control we will have of the problem. Risk management plans that ignore the physician are doomed to failure.

Summary

Opioids have been proven to increase functioning and quality of life in patients with chronic pain. Proper pain treatment can reduce its enormous economic, social, and personal costs. However, opioids have risks associated with their use, including abuse and misuse, addiction, side effects such as respiratory depression, and diversion.

The professional organizations AAPM and APS published a consensus statement in 1997 that stated the above points and then designed a plan to maximize proper use while minimizing the risks. The plan involves publishing guidelines for opioid use, physician training, patient education, and monitoring to ensure that the plan is working correctly. Proper documentation of every step in the process is also crucial.

Risk management plans based on this and other statements have been developed for many opioid drugs since that time. The goals of these plans are proper product labeling, effective monitoring and surveillance, and education of physicians and patients in the use and risks of opioids. If these goals are met, a risk management plan can minimize those risks and optimize pain treatment.

Review Questions (I)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. Publishing clinical practice guidelines for opioid use accomplishes all of the following goals, **except**

   a. helping ensure that opioids are used properly.

   b. letting police know when laws are being broken.

   c. letting regulators distinguish accepted practice from unaccepted practice.

   d. providing physicians with information on which to base treatment decisions.

2. The risks of opioid use include all of the following, **except** for

   a. abuse and misuse.
   b. addiction.
   c. diversion.
   d. tolerance.

3. Which of the following topics is **not** a part of a well-written package insert?

   a. appropriate dosing
   b. common/serious side effects
   c. how to take the product properly
   d. legal ramifications of improper use

Check your responses on page __.

II. THE ENDO RISKMAP PROGRAM

The Endo RiskMAP program is based on the ideas put forth in the AAPM/APS consensus statement and other risk management programs that have been developed since that time. Its main strategies include product labeling; education of patients, caregivers, and healthcare professionals; and other strategies such as postmarketing surveillance and distribution oversight.

In this section we will concentrate on the package insert and the many educational programs developed and/or sponsored by Endo to heighten awareness of the risks of long-acting opioids like OPANA™ and to teach everyone involved the proper use of these drugs. The next section will discuss the other strategies for achieving the goals of the RiskMAP program.

Learning Objectives

1. State the purpose of the patient package insert (PPI).
2. Identify the elements that should be included in opioid-related education programs.
3. State the objectives of the programs to educate Endo sales and marketing staff on appropriate and responsible selling.

Key Concepts

1. The PPI translates the complicated language of the package insert (PI) into simpler language and explains complicated scientific concepts. This ensures that all patients will understand the important information provided in the PI.
2. Opioid-related education programs should include information on many subjects. These should include careful selection of patients, patient assessment and reassessment, identification of patients at higher risk for abuse, appropriate documentation, actions for minimizing risk of abuse or accidental exposure,

and differentiation among physical dependence, tolerance, and addiction.

3. The objectives of training the Endo sales and marketing staff include familiarizing them with basic concepts of risk management, the laws governing their relationships with providers, the legal guidelines of the use of controlled substances and potential liability, and was to show providers how to access additional resources on these issues.

A. Product Labeling

Endo will continue to work with the Agency to develop approved product labeling that adequately instructs healthcare providers and patients in the safe and appropriate use of the product. The Package Insert (PI) will also contain the appropriate language needed to inform healthcare providers and patients of the risks associated with the product and the information required to help minimize the risk of abuse, misuse, and diversion.

Endo has submitted a Patient Package Insert as part of the proposed labeling for oxymorphone ER. The Patient Package Insert translates the Package Insert into terms understandable by a typical patient (approximately a sixth-grade level). The oxymorphone Patient Package Insert contains the following information.

- Most important information regarding the medication
- Accidental overdose by children
- Co-ingestion with alcohol
- Side-effects of the treatment

A PPI will be produced as part of the package labeling for OPANA™. This insert will translate the sometimes complicated language of the PI into simpler language and will explain the more complex scientific concepts so that patients can more easily understand safety concerns with the drug. This is designed to help prevent potential problems due to patient confusion.

B. Education

Endo has developed and implemented, and will continue to support the development and implementation of, educational initiatives for physicians, pharmacists, nurses, and other allied healthcare professionals on the appropriate use of opioid analgesics with a particular emphasis on modified-release opioids. Educational initiatives for patients, their families, and caregivers will emphasize safe and appropriate use as well as discuss resources to contact for further assistance with questions and concerns regarding opioid medication use.

Although the sponsor funds these educational programs through unrestricted educational grants, and thus relinquishes control of content to the authors, faculty, and CE providers, the Sponsor will stress the requirement for discussion of risk management and request that the following elements be considered in the planning of all opioid-related programs.

- Careful selection of patients for whom a modified-release opioid is appropriate (type and duration of painful condition)
- Initial assessment of patient including pain assessment tools prior to initiation of therapy with a modified-release opioid
- Regular reassessment of patient once therapy is initiated
- Identification of patients at higher risk for abuse and diversion, and available management tools for this special population
  - Screening tools (e.g. SOAPP)
  - Patient-physician agreement
  - Frequency of follow-up
  - Role of drug screening to monitor compliance
- Appropriate ongoing documentation for patients prescribed a long acting opioid
- The importance of patient and family/caregiver education
- Actions for minimizing the potential risk for abuse and misuse
- Action for minimizing the potential risk of accidental exposure
- Differentiation among states of physical dependence, tolerance, pseudoaddiction, and addiction

- Avoiding co-ingestion with alcohol
- Tapering off opioid therapy in patients for whom opioids have proven unhelpful

Professional and patient education initiatives with risk management components include but are not limited to those described in the following sections.

Educational programs designed to teach healthcare professionals, patients, and caregivers are being developed under the aegis of Endo. These programs will stress the teaching of risk management including proper patient selection, methods for minimizing abuse and accidental exposure, regular reassessment of patients, and proper use of the drug. The programs are designed to ensure that all people involved in pain management with OPANA™ will be aware of its proper use and the risks associated with misuse.

1. Professional Education Initiatives.

The "National Initiative on Pain Control" (NIPC) is a CME-accredited educational program solely supported by Endo, which was established to advance clinicians' understanding of pain assessment/treatment, and to improve outcomes for patients with chronic pain. These programs are based upon a common slide kit developed by the NIPC Education Council, an educational advisory group of thought leaders in the area of pain management and opioid pharmacotherapy for the treatment of pain who are solely responsible for curriculum content and development. Once the curriculum has been developed, a core group of faculty is trained by the Education Council and the CME sponsor to deliver the programs. The faculty consists of physicians, nurses and pharmacists with an established expertise in the diagnosis and treatment of chronic pain, including the appropriate use of opioid analgesics.

The intended audience for the NIPC initiatives includes 60,000 internists, family physicians, osteopathic medicine specialists, general neurologists, physical medicine and rehabilitation specialists, and other clinicians who manage patients with chronic pain.

To date, the following two live-CME modules, specifically addressing the responsible prescribing of opioid analgesics, have been developed for the NIPC curriculum:

- "Opioid Analgesia: Practical Treatment of the Patient with Chronic Pain"

- "Advances in Opioid Analgesia: Maximizing Benefit; Minimizing Harm"

These modules have also been integrated into a half-day symposium format entitled:

- "Optimizing Patient Outcomes in Pain Management: New Strategies for Today's Clinical Practice"

In addition, an audioconference module has been developed to extend the reach of the opioid education initiatives and for physicians unable to attend.

- "Opioid Analgesia: Enhancing Pain Management and Patient Outcomes"

This module may also be utilized in rural or difficult to access geographies, or can be tailored by the CME provider for use in targeted interventional areas.

The NIPC programs have been supported through an unrestricted educational grant from Endo since the initiative's inception in 2001; Endo is the sole grantor supporting the NIPC and plans to continue grant support for NIPC indefinitely. For 2005/2006, the opioid educational initiatives will be offered via various educational media such as:

- CME-accredited Dinner Dialogue™ Programs
- CME-accredited Audioconferences
- CME-accredited half-day symposia
- CME-accredited newsletters
- CME-accredited Webcasts

During 2005/2006, these programs will be implemented and will educate clinicians nationwide on proper patient assessment, selection, and follow-up with regards to the use of modified-release opioids for the treatment of chronic pain. In addition, Endo has suggested to the CE provider that programs appropriate for pharmacists be added to the curriculum.

A number of programs have been developed for continuing education of healthcare professionals in pain assessment and treatment. These programs were developed by thought leaders in the field and are available in a number of formats to allow easy access to all.

The following materials that have been developed to date for the NIPC opioid analgesic modules include:

NIPC Core Curriculum/Faculty Guide
The NIPC core curriculum/faculty guide consists of all core curriculum slides, speaker notes, and references utilized by the NIPC visiting faculty. This guide describes the learning objectives, reviews the ACCME requirements, and includes the curriculum materials and references.

NIPC Participant Guide
This guide is provided to every participant in the live CME-accredited lectures and symposia. The purpose is to reiterate the CME learning objectives, to provide hard copies of the core curriculum slides, and to provide space for participants to record notes on the faculty presentations. Each participant guide also contains a copy of the CD-ROM resource kit, which the clinician can utilize to improve patient management. The kit includes an innovative patient care algorithm designed to simplify opioid prescribing for the primary care physician. The algorithm emphasizes previously neglected areas of opioid management including management of side effects, assessment of abuse, and exit strategies from opioid therapy when appropriate.

This program will aid clinicians with appropriate patient selection and promote safe opioid use.

NIPC Audioconference Guide
This guide is provided to all registrants in the interactive audio conferences. The audioconference guide provides a means for the participants to view the core curriculum slides at their desks, while participating in the interactive audioconference. Each audioconference guide also contains a copy of the CD-ROM clinician resource kit.

NIPC Pain Management Today Newsletter
The NIPC ***Pain Management Today*** newsletter is a 12 page CME-accredited publication distributed bi-annually to 60,000 physicians who manage chronic pain patients. The publication is intended as a resource, which provides timely articles of clinical importance, patient assessment/management resources, case studies, and a clinical Q&A forum on chronic pain.

The Office of Women's Health of the US Department of Health & Human Services: "Breakthroughs & Challenges in the Management of Common Chronic Pain Disorders" Initiative
National CME-accredited initiative presented by the Office of Women's Health (OWH) Department of Health and Human Services (HHS), and chaired by Richard Payne, MD and Christine Miaskowski, RN, PhD, two nationally-recognized experts in the field of pain management and opioid analgesics.

The initiative consisted of a 3-day faculty meeting to discuss the most recent advances in managing chronic pain, followed by the development of a slide curriculum and a series of enduring materials, which are being disseminated under the auspices of OWH/HHS and various national professional societies.

A substantial portion of the curriculum focuses on the responsible use of opioid analgesics for chronic pain disorders, including clinical and risk management considerations. The target audience for the educational materials is family physicians, internists, neurologists, anesthesiologists, physical medicine and rehabilitation, and other clinicians who treat chronic pain. The first in a series of enduring materials from this meeting was published and distributed in 3Q 2004; additional enduring materials were distributed in 2005 and updates are planned for2006.

Satellite Symposia & Initiatives in Collaboration with Professional Societies

Endo recognizes the importance of peer-to-peer education via national congresses and professional societies as a means of advancing clinicians' knowledge about the responsible prescribing of opioid analgesics. To this end, Endo has and will continue to support satellite symposia and educational programs in conjunction with professional congresses or societies such as:

- American College of Physicians (ACP)
- American Academy of Family Physicians (AAFP)
- Society of Teachers of Family Medicine (STFM)
- American Pain Society (APS)
- American Academy of Pain Medicine (AAPM)
- American Academy of Pain Management
- American Society of Addiction Medicine
- Annual Conference on Pain & Chemical Dependency
- PriMed Primary Care Regional Education Conferences
- Multi-National Association for Supportive Care in Cancer
- American Society of Pain Management Nurses
- Oncology Nursing Society
- American Society of Health System Pharmacists
- Academy of Managed Care Pharmacy
- Other regional pain education symposia

These symposia and initiatives are scheduled in conjunction with the above-listed Congresses, and/or professional society meetings. Again, these satellite symposia are funded through unrestricted educational grants provided to the professional societies or CE providers. The Sponsor will continue to make the organizers aware of the need for balance on the issues of risk management.

Physician-in-Training and Primary Care Initiatives

Endo recognizes the need to educate physicians-in-training and primary care physicians on appropriate pain assessment, responsible prescribing of opioid analgesics and appropriate patient follow-up which optimizes pain relief while minimizing the potential for adverse events, including medication misuse.

The following programs, supported through unrestricted educational grants from Endo, focus on these key groups of clinicians:

- American Pain Society (APS) Residents Course – an annual 2-day course taught to approximately 100 residents from family medicine, internal medicine, neurology, anesthesiology, physical medicine/rehab, and emergency medicine. Several hours of the course focus on opioid-related issues including: appropriate patient selection, practical prescribing considerations, side effects, patient follow-up and documentation, and addiction/dependence/abuse/diversion issues. Endo initiated this course 4 years ago and has been the sole supporter for the course every year since via an unrestricted educational grant to Northshore/Long Island Jewish Health System. This course takes place annually prior to the APS Meeting.

- American Academy of Family Physicians (AAFP) – a 3 hour AAFP evidence-based CME video and educational monograph entitled "Managing Pain: Dispelling the Myths." This monograph, which has been distributed to all AAFP members, examines the appropriate assessment and management of pain, including: responsible use of opioid analgesics, discussion of controlled substances, abuse, addiction, pseudoaddiction, physical dependence, and tolerance.

- Society of Teachers of Family Medicine (STFM) – for the past 3 years Endo has supported a full day pre-course at this annual meeting for family medicine faculty and residency program directors. The course, developed and presented by the STFM's Pain Management Interest Group, focuses on the essential principles and practice of pain assessment and management. A substantial amount of didactic and interactive discussion time is focused on the appropriate prescribing of opioid analgesics, clinical considerations, and abuse/misuse/addiction/diversion issues. This course occurred in 2004 and 2005; a similar initiative is planned for 2006.

- California Primary Care Course – 12 hour CME-accredited course developed to educate primary care physicians in California on the principles/practice of pain management, including several hours related to appropriate prescribing of opioid analgesics, appropriate patient selection, proper education and follow-up, and addiction/abuse/diversion issues. Endo is the sole grantor for this Course which was offered in 2003–2005; a similar program is planned for 2006.

- American College of Physicians (ACP) – 3-hour workshop on Pain Management at the national ACP meeting. A substantial portion of this workshop for internists focuses on the appropriate use of opioid analgesics, patient selection and follow-up and addiction/abuse/diversion issues. This Workshop took place during 2004; during 2005, an enduring material was published/distributed to all ACP members. Additional pain management initiatives with the ACP are planned for 2006.

- PriMed Conferences – symposia at these annual meetings of primary care physicians have occurred for the past two years and are planned for 2006. Significant time is devoted to appropriate prescribing of opioid analgesics, as well as side effects and the potential for misuse/diversion. Following the conference, CME-accredited enduring materials are distributed to primary care physicians.

Endo plans to continue the above initiatives, or similar educational initiatives during 2005/2006.

Symposia have been developed in conjunction with a number of professional societies for peer-to-peer education in pain management. These allow professionals to learn the most up-to-date information on the responsible use of opioids in pain management from the experts in the field. Participant guides, CD-ROMs, and newsletters allow the participants to review what they have learned and continue their education long after the symposium is over.

www.Painedu.org Website and Manual

This initiative consists of a website and pocket manual created by Inflexxion, a science-based, interactive healthcare technology company. Inflexxion develops web-based programs for clinicians and consumers. It also develops and tests clinical measurement scales and assessment tools. As well as providing programs and services to healthcare and substance abuse organizations around the country, Inflexxion works extensively with the pharmaceutical industry and in particular companies with pain products. *PainEdu* utilizes nationally-recognized experts within the behavioral health, oncology, pain medicine and addiction medicine fields to develop content for both the website and the pocket manual.

The site is highly interactive and makes use of case-based learning, roundtable discussions, 'ask the expert' modules, downloadable tools such as the SOAPP, an electronic download of the Clinical Companion manual and makes use of varied educational strategies. Further, *PainEdu* provides online continuing education credits to physicians, psychologists, nurses and pharmacists. The site is used actively by healthcare professionals and has nearly 6,000 registered users as of October, 2005. It has received an award for provider education excellence and was cited by the APS Newsletter as a very valuable resource.

For the past four years, Endo has supported the development, maintenance and continued enhancement of *PainEdu* through an unrestricted educational grant.

PainEdu.org is a website dedicated to interactive web-based programs for continuing education in pain management. A variety of educational tools are utilized to promote active learning, a method proven to be effective in adult learning.

ACPE-Accredited Pharmacy Education Monographs

Endo has supported the development of ACPE-accredited monographs to educate pharmacists on the proper role of modified-release opioid analgesics for the treatment of chronic pain. These educational materials discussed the clinical/risk management considerations, and stress the importance of the relationship between the prescribing physician and the pharmacist in detection of abuse or diversion of opioid analgesics.

The monographs were distributed to all pharmacy specialties, including retail independent, retail chain, consultant pharmacists, hospital pharmacists, and HMO-based pharmacists via national pharmacy practice publications. The accredited programs will also be available for 2 years from that date on the publications' websites. There are subsequent publications planned to assure that pharmacists receive these critical education materials on a going forward basis via various pharmacy education publications/websites.

In addition to these continuing education materials, The Sponsor will provide pharmacies with patient education tools similar to the materials provided to physicians that allow for discussion between the pharmacist and patient on the appropriate use of modified-release opioid analgesics at the point of dispensing. (See Patient and Family Education Section below.)

Strengthening the link between physicians and pharmacists is important for detecting and minimizing abuse or diversion of opioids. Providing pharmacists with the same information available to physicians concerning proper use of opioids allows pharmacists to answer questions more effectively. This can only help to ensure that patients get all the information they need to use the opioids safely and effectively.

"Practitioner's Guide to Prescribing Opioid Analgesics for Persistent Pain" Handbook
This practical clinical handbook was authored by Russell Portenoy, MD and Perry Fine, MD, two nationally-recognized experts on opioid analgesics and published by McGraw Hill. The handbook is intended to provide the essential information necessary for clinicians to responsibly prescribe opioid analgesics for persistent pain, including both clinical and risk management considerations. Development and dissemination of the handbook has been supported through an unrestricted educational grant from Endo; hard copies of the book have been distributed since mid-2004, and during 2005, an electronic version was posted to the nationally-renowned www.stoppain website.

"Advances in Cancer Pain: A Bedside Approach" Handbook
This handbook, authored by Ann Berger, RN, MD, Chief of Pain and Palliative Care Service at the National Institutes of Health (NIH), and published by The Oncology Group, is intended to provide practical, clinical information on the assessment and treatment of cancer pain. The handbook has been made available to both primary care clinicians and oncology specialists/nurses via an unrestricted educational grant from Endo. At least half of the handbook focuses on the appropriate prescribing of opioid analgesics, including both clinical and risk management issues. The book has been available since 3Q 2004.

"Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain"
This handbook was prepared by a multidisciplinary committee of the APS to disseminate current information on effective therapy for acute pain and cancer pain to a broad audience of clinicians. Over 50% of the handbook focuses on the appropriate use of opioid analgesics including: dosing and compliance information; adverse effect recognition/treatment; and tolerance/addiction/ dependence issues. Endo makes this handbook available through its Scientific Affairs Department.

Risk Management Information/Tools for Clinicians
The Sponsor will provide clinicians with risk management information and risk management tools recommended by recognized experts in the fields of pain management and addiction medicine. Planned for inclusion are educational materials for patients and clinicians, a prototype patient/physician pain management agreement, and tools for assessing the patient's relative risk for misusing/abusing their medication.

AAPM/APS "Consensus Statement on the Use of Opioids for the Treatment of Chronic Pain"
This joint consensus statement was prepared by the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) to provide guidance to clinicians on the under treatment of pain; to provide clarity on issues of addiction, diversion, tolerance, and side effects; and to promulgate principles of good medical practice with regards to the use of opioid analgesics for chronic pain. Endo has purchased quantities of the Consensus Statement which are made available through its Scientific Affairs Department.

A number of handbooks and printed materials have been developed for educating physicians on appropriate prescribing and use of opioids, risk management programs and plans, and the issues surrounding addiction, tolerance, and diversion. These printed guides give the physicians a way to keep current on these issues on their own schedules.

2. Patient and Family Education.

Patient and Family Brochure-"Understanding Your Pain: Taking Oral Opioid Analgesics"

This patient/family education brochure, supported by an unrestricted educational grant from Endo, was authored by Margo McCaffery, RN and Chris Pasero, RN, and edited by Russell Portenoy, MD. The brochure is intended to be provided to physicians and pharmacists for their patients being considered for or currently taking oral opioid analgesic therapy.

The brochure provides information to patients and family members on: opioid analgesics; their role in pain management; their potential side effects; information on addiction in patients taking opioids for the management of pain; and patient information on how to take their medication and track their pain. The booklet is available through the Endo sales force, the Scientific Affairs Department and the Endo corporate website, as well as at professional society meetings and educational conferences, including national pharmacist meetings such as the American Society of Health System Pharmacists, the Academy of Managed Care Pharmacy, and the American Society of Consultant Pharmacists. The brochure has been available in both print and electronic versions since 2Q 2004.

Pain Assessment Inventory and Patient/Family Education Materials

Since 2000, Endo has provided tear pads, which include the Brief Pain Inventory (BPI) and accompanying educational information on pain and pain assessment to physicians for their use in educating patients.

Upon publication of the national standards for pain assessment and management by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), Endo supported the development of another patient/family education brochure entitled "Understanding Your Pain: Using a Pain Rating Scale." This brochure, developed through an unrestricted educational grant, was authored by Margo McCaffery, RN, Chris Pasero, RN, and edited by Russell Portenoy, MD. The brochure was endorsed by the JCAHO and has been distributed since 2001 in both print and electronic versions under the joint logo of JCAHO and Endo.

During 2004/2005, Endo developed and disseminated additional patient/family education pieces such as the aforementioned brochure on opioid analgesics, as well as materials, which stress the importance of compliance with opioid analgesic treatment regimens. Patient/family education pieces are also planned for 2006. Oxymorphone-specific materials will include any warnings and precautions from the Product Information with respect to appropriate dosing, potential side effects and their management, and the risks associated with modified-release opioids when they are inappropriately used by someone other than the patient for whom they were prescribed.

In addition, Endo will continue to support the development and distribution of patient/family education materials through national patient organizations such as the American Pain Foundation, the National Pain Foundation and the American Chronic Pain Association.

Patient education is at least as important as physician education when it comes to risk management. Separate educational materials are needed for patients, since they are generally starting from a much lower level of knowledge on the subject. The information must be presented in a more straightforward way and avoid using technical language as much as possible.

The brochures listed above explain warnings and precautions of opioid use, potential side effects, and addiction and tolerance. This allows the patient to be informed about his or her own treatment and is designed to reduce the risks that accompany ignorance.

Pain Action
In December of 2005 Inflexxion, with support from Endo and NIH, will launch *PainAction.com*. This site will be consumer-oriented and will provide patients and families with a variety of ways to become better informed about and better able to cope with their pain-related problems. It will also contain educational materials on the safe and appropriate use of opioids, self-assessment tools for patients to assess their relative risk of developing aberrant drug-related behaviors, proper storage and disposal information, and the importance of avoiding co-ingestion with alcohol and other specific drugs. Experts from the consumer side of pain management will consult on this project.

Consumers will also have the opportunity to utilize a variety of interactive tools (e.g., pain and symptom diaries) and self-report measures to be better able to consider how they can actively participate in their pain care. *PainAction* will be one of the most extensive consumer-oriented web programs focused on pain available on the Internet. In addition to Endo's educational grant support for the overall site, Inflexxion has received and will receive funding from NIH to further develop and test particular disorder-focused (e.g., back pain) components of *PainAction*. It is also likely that *PainAction* and *PainEdu* will be synergistic (i.e., pain clinicians will refer their patients to *PainAction* and consumers may recommend *PainEdu* to their clinicians).

As with physicians, patients can benefit from the interactive learning available through web-based programs. Patients can learn on their own through the site, which can give them a sense of control and empowerment that they may not feel when talking to their physician.

3. Validated Tools.

Screener and Opiate Assessment for Patients with Pain (SOAPP)
Endo is currently supporting and will continue to support the development of what is referred to as the SOAPP tool – a prospective, patient self-report screening tool funded by grants from National Institute on Drug Abuse (NIDA), and developed by a team from Harvard University, Brigham and Women's Hospital, and Inflexxion, a healthcare research company with expertise in development of screening tools. With support from Endo, Inflexxion developed and rigorously tested Version 1 of SOAPP. At present they are expanding their SOAPP research with NIDA support to a much larger sample and making additional modifications on the scale that will be integrated into Version 2.

The SOAPP tool is a brief screening, self-report tool for those chronic pain patients being considered for opioid therapy. It will be easily completed and scored in less than 10 minutes in the waiting room of a physician's office or alternatively could be completed prior to the visit either as a brief paper questionnaire, online, or through an Interactive Voice Recognition (IVR) system. Such a tool could help classify patients along a continuum of greater or lesser likelihood of encountering misuse-related problems during a regimen of opioid medications. This information, along with interpretive cutoffs, would inform the healthcare provider that a given patient may require extra monitoring while on pain medications or perhaps, that additional or alternative treatments should be considered.

Version 1 of SOAPP has already been the subject of a scientific publication as well as a number of professional society presentations. At present, the SOAPP Version 1 is being utilized by private physicians and in clinics as well as pharmacies; it is anticipated that this usage will increase significantly over the next year.

Appropriate patient selection is a key to reducing the risks associated with opioid treatment. The SOAPP tool is a brief questionnaire designed to determine whether a patient is more or less likely to misuse opioids. This information would allow a physician to design a pain management program for a higher-risk patient that either does not use opioids or that includes extra monitoring to uncover any misuse.

4. Sales Force Training.

Endo fully understands the importance of responsible commercialization of this newly extended release opioid. An essential part of the approach will be to ensure our sales representatives are optimally prepared to provide physicians with the appropriate information supported by the approved label. Sales force training will be comprised of didactic and self-study modules as described below. Information regarding sales force compliance is also described below.

Therapeutic Class (Opioids and TRADEMARK-specific) Training
Endo's sales force will undergo extensive training to assure that there is a clear understanding of the appropriate use of modified-release opioids, including the types of patients for which these medications are indicated, the physicians who treat these patients, and the laws and regulations that govern the use of CII controlled substances. Endo's sales representatives will also be trained on the appropriate use of TRADEMARK, the use of educational tools developed for physicians, pharmacists, patients and caregivers, the adverse event profile of opioids as a class and the potential for abuse/misuse/diversion. The sales force will provide professional educational materials developed by the Sponsor to physicians and other healthcare professionals who request them.

Therapeutic class training for the sales force includes: 1) the neuroanatomy of pain; 2) physiology of pain; 3) common etiologies of chronic and breakthrough pain; 4) pain assessment; and 5) pain management and the analgesic marketplace.

Appropriate and Responsible Selling of TRADEMARK
Endo will conduct extensive training of its sales force, using a combination of self study/assessment tools and classroom training on the appropriate use of TRADEMARK (the Outline of this sales training program is provided in Appendix 1; detailed training content is under development and will not be finalized until final Product Information is approved by the FDA). Sales representatives will be required to demonstrate their understanding of the approved prescribing information and the potential risks involved with improper use or abuse of TRADEMARK through a written assessment prior to calling on physicians.

The objectives of the program are: 1) To familiarize Endo's sales and marketing staff with basic concepts of risk areas and risk management related to the promotion and sales of TRADEMARK; 2) To ensure Endo's sales and marketing staff achieve a basic understanding of the laws governing relationships between pharmaceutical companies and their representatives and members of the provider communities; 3) To familiarize Endo's sales and marketing representatives with legal guidelines on pain management and the use of controlled substances to treat pain; 4) To provide Endo's sales and marketing representatives with specific examples of personal conduct that can create legal liability, including conduct related to off-label marketing of TRADEMARK and improper relationships with providers and to familiarize Endo's sales and marketing representatives with additional legal liability issues relating to provider detailing, CME activities, and written marketing materials; 5) To insure a basic understanding of potential legal liability for providers who manage pain and use controlled substances to treat pain and to understand Endo's role in working with providers and patients to minimize the potential abuse and diversion of TRADEMARK; and 6) To learn to show providers how to access and use the provider toolkit documentation and how to locate additional resources on these issues.

The sales force will play an important role in dissemination of educational tools, which aid in the appropriate use of TRADEMARK. The Sponsor believes that this proactive approach will help those providers who prescribe TRADEMARK to understand patterns and behaviors suggestive of patient opioid misuse, abuse, and diversion. The Sponsor's message in these interventions will be one of cultivating accountability regarding the proper use of TRADEMARK.

The sales force is an important source of information about any drug. They must therefore know not only all the risks involved with the drug, but also the legal guidelines that govern the use of opioids to minimize misuse and diversion. Self-study and classroom training tools are being developed to ensure that the representatives will learn what they need to know. Assessment tools will then determine whether they have done so. A well-educated sales force can help identify misuse and diversion and will feel accountable to avoid such problems.

Sales Force Compliance

The Sponsor intends to monitor the compliance of the sales force with approved marketing and sales guidelines in two ways. District sales managers, who will be thoroughly trained, will spend time in the field with each representative to assess the accurate delivery of appropriate messages and take corrective action with additional training, coaching, etc. to remedy the situation, if needed. The Sponsor will also utilize market research to monitor healthcare providers' comprehension and interpretation of promotional messages. If needed, the Sponsor can make adjustments to its sales training curriculum to diminish the likelihood of promotional message misinterpretation.

The Sponsor's sales representatives will have a responsible incentive/commission plan that is in line with industry standards. In order to qualify for the incentive compensation, each representative must be initially certified and annually re-certified on the education program. The Sponsor's sales representatives will make sales calls on physicians who treat patients for whom a modified-release opioid is appropriate. The target audience includes pain specialists, oncologists, advanced practice oncology and pain management nurses, rheumatologists, physical medicine/rehabilitation specialists and primary care physicians who treat significant populations of moderate to severe chronic pain patients and are experienced prescribers of modified-release strong opioids.

The content outline for Endo's Pain Management and TRADEMARK Learning Systems is presented in Appendix 1. The intent of these programs is to create a sales force with extensive knowledge on the subjects of pain, pain treatments, healthcare providers who treat pain, benefits and risks of opioid pain medications and applicable laws, regulations and policies.

Compliance of the sales force with the marketing and sales guidelines set out in the training program will be ensured in two ways. District sales managers will assess each representative's performance in the field to ensure that they are accurately disseminating information. Marketing data will also be collected to ensure that the proper messages are being communicated to healthcare professionals.

Summary

Product labeling includes both a PI and a PPI. The PI is a scientific document that instructs healthcare providers and patients in the safe and appropriate use of the product. The PPI translates the complicated language of the PI into simpler language and explains complicated scientific concepts to ensure safe and effective use of the product.

Opioid-related education programs should include information on many subjects, including careful selection of patients, patient assessment and reassessment, identification of patients at higher risk for abuse, appropriate documentation, actions for minimizing risk of abuse or accidental exposure, and differentiation among physical dependence, tolerance, and addiction. Many different types of education programs are available. Symposia, workshops, websites, and written materials can all be used to get the information to people who can benefit from it.

One group that it is important to educate is the Endo sales and marketing staff. Self-study/assessment and classroom training followed by written assessment will teach the basic concepts of risk management, the laws governing their relationships with providers, the legal guidelines of the use of controlled substances and potential liability, and ways to show providers how to access additional resources on these issues.

Review Questions (II)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. The patient package insert for OPANA™ will include all of the following information from the PI, **except** information on

   a. accidental overdosage by children.
   b. co-ingestion with alcohol.
   c. indications for treatment.
   d. side effects.

2. Opioid-related education for physicians should include all of the following topics, **except**

   a. appropriate documentation.
   b. careful patient selection.
   c. patient assessment.
   d. use of surveillance databases.

3. Which of the following methods will **not** be used to ensure that the Endo sales force is compliant with sales and marketing guidelines?

   a. district sales managers traveling with the representatives

   b. monitoring healthcare provider's comprehension of messages

   c. monitoring rates of abuse in each sales representative's territory

   d. self-study and classroom training

Check your responses on page __.

III. Other Strategies and Tools

Education is an important part of reducing the risks of opioid therapy; however, it is still important to monitor the use of the drug to ensure that the education is working correctly and to identify individuals who are not interested in education but only in obtaining the drugs for other uses.

Tools for preventing diversion of opioids include tamper-resistant prescription pads, oversight of the distribution chain so that all of the manufactured drug is accounted for at all times, and postmarketing surveillance through a number of avenues to detect any misuse of the drug. This section will describe the tools to be used in the Endo RiskMAP.

Learning Objectives

1. State the purpose of Endo's periodic reports on postmarketing surveillance.
2. Identify databases that can be used for postmarketing surveillance.

Key Concepts

1. Endo's periodic reports on postmarketing surveillance will include information on adverse events reported with OPANA™. It will be sent to the Endo Safety Review Board (ESRB) to analyze trends indicating abuse, misuse, or overdose.
2. Databases that will be used for postmarketing surveillance include NAVIPPRO, TESS, DAWN, IMS Health Xponent, and QISP.

A. Tamper-resistant Prescription Pads

Prescription fraud, the alteration, forgery, or counterfeiting of a prescription is a common means of diversion in the US. Endo will provide tamper-resistant prescription pads to prescribers, free of charge, to help protect healthcare professionals and patients from criminal drug diverters who attempt to illegally obtain controlled medications. These pads include several security features intended to help prescribers and pharmacists recognize and thwart common types of prescription fraud.

Tamper-resistant prescription pads can help prevent forging and altering written prescriptions. All prescriptions of Schedule II drugs must be written, so these pads will provide a powerful tool to reduce opioid diversion.

B. Oversight of the Distribution Chain

As for all of Endo's controlled substance products, the manufacturing and distribution chain is highly controlled and closely monitored. Endo employs sophisticated controls and monitoring at its manufacturing sites, in transit to Endo's distribution center, at the distribution center, and in transit to the wholesalers and large retail chains with appropriate CII vaults. All of Endo's manufacturing and distribution sites are rigorously inspected by the Drug Enforcement Agency (DEA) and all have close working relationships with their respective law enforcement agencies.

Endo's oversight includes physical and administrative controls as well as significant monitoring activities. Endo's physical and administrative controls at the manufacturers and distribution sites meet or exceed DEA requirements for CII materials. Endo's typical manufacturing and distribution chain controls are shown in Appendix 2; order management practices are presented in Appendix 3. Detection techniques, such as undercover security personnel and random checks, are employed in many cases. In addition, order management and transaction data are monitored frequently to look for unusual changes in deliveries to customers. For example, order and delivery discrepancies are tracked weekly and trends identified where discernable. These discrepancies may include events such as shortages, damage, and late deliveries. When trends are observed, actions are taken which may include changes in commercial carriers, personnel, outer packaging, and delivery schedules. Additional monitoring of specific or anonymous complaints is performed through Endo's external website and customer service email address.

Manufacture and distribution of Schedule II drugs is monitored by the DEA to avoid diversion. A variety of monitoring techniques are used to oversee the process. The DEA guidelines are built on many years of experience and are designed to thwart known methods of diversion.

C. Postmarketing Surveillance

Endo's Pharmacovigilance and Risk Management Department will conduct proactive surveillance of EN3202/03 adverse event reports received via post-marketing surveillance (spontaneous reports, scientific literature, post-marketing clinical investigations, and postmarketing epidemiological surveillance studies). Endo will review, investigate, process, and track adverse events for safety surveillance and safety signal detection. Reports of all serious adverse events to the FDA will be submitted in accordance with the current Federal Regulations.

1. Periodic Reports.

Endo will assemble and submit periodic reports for all adverse events received for EN3202/03 in accordance with current Federal Regulations. The periodic reports will be submitted on a quarterly basis for the first three years of marketing and yearly thereafter. These reports will be reviewed by Endo's Safety Review Board (ESRB) for trending and signal detection, specifically for increased reports of abuse, misuse or overdose.

By keeping track of adverse events with OPANA™, Endo can identify and react to trends that signify abuse or misuse of the drug. Reports will be more frequent for the first 3 years after marketing to establish a solid baseline from which changes can be recognized.

2. Secondary Databases.

National Addictions Vigilance Intervention & Prevention Program. Inflexxion is developing a national drug monitoring system for prescription and non-prescription drugs of abuse that will enable pharmaceutical companies, regulatory authorities and other customers to have immediate access to valid and reliable data about the abuse and misuse of specific medications throughout the US. This system, called the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), will provide companies with real-time product-specific medication data from an independent, scientifically-based third party. This will allow companies and regulatory agencies to identify abuse issues regarding particular products at an earlier point than what is available with current monitoring systems. NAVIPPRO will also

examine comparative data and will be able to differentiate abuse and misuse of different brands and formulations. Among the unique, state-of-the-art features that are part of NAVIPPRO is the real-time reporting of product specific data as well as the application of statistical process control (SPC) methodologies to detect and localize signals of abuse and misuse. To our knowledge, NAVIPPRO will be one of the first systems to make SPC approaches a core analytical tool of a prescription drug risk management program.

The surveillance component of NAVIPPRO is being developed using an Internet version of Inflexxion's previously released CD-ROM based Addiction Severity Index – Multimedia Version (ASI-MV). The ASI-MV was researched and developed with National Institute of Drug Abuse (NIDA) support and is now being used at over 600 substance abuse treatment centers around the country. The Internet version of the ASI-MV, which will be a part of NAVIPPRO, is referred to as ASI-MV Online.net. The ASI-MV Online will expand upon the standard ASI-MV and will include questions and graphics designed to identify prescription drug problems and trends. Audio and video components of the Internet ASI-MV.net will be designed to assist respondents in accurately identifying prescription drugs used and in reporting their experience, including data such as specific illnesses, pain and medical treatment. In addition, questions will be added that seek to determine the sources of the medication taken by the respondent and pathways to abuse. To date, there have been about 250,000 administrations of the ASI-MV around the country. It is believed that using the ASI-MV Online as part of NAVIPPRO will increase the ASI-MV usage even further and provide Inflexxion and hence Endo and other companies with extensive, real-time product specific data and signal detection capability that is well beyond current data sources.

NAVIPPRO will help fulfill the vision of the FDA Advisory Committee in September, 2003, by providing detailed information for the first time on what proportion of patients entering substance abuse treatment are patients with pain, whether they had addiction-related problems prior to therapeutic or non-therapeutic opioid exposure, what the sources are of diverted prescription opioids, and what are the risk factors for developing prescription opioid abuse.

Toxic Exposure Surveillance System (TESS). Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC) in cooperation with the majority of US poison centers. These data are used to identify hazards early, focus prevention education, guide clinical research, and direct training.

Endo will review the AAPCC annual report to identify EN3202/03 exposures. Endo will then order abstracts for exposure and fatality cases associated with EN3202/03. The abstracts contain the following information: case number, patient's age, suspected substance(s), chronicity of the event, route of administration, reason for taking the suspected substance(s), and brief narrative surrounding the event. These reports will be analyzed, entered in the safety database, and reported to the Agency in accordance with Federal Regulations.

Drug Abuse Warning Network (DAWN). The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related emergency department visits for the Nation and for selected metropolitan areas. DAWN also collects data on drug-related deaths investigated by medical examiners and coroners in selected metropolitan areas and States. The new DAWN implemented in 2003 now casts a wider net, and collects more details about each case. Please note that the new DAWN and its estimates for 2003 are not comparable to those for any prior years. DAWN is operated by the Substance Abuse and Mental Health Services Administration (SAMHSA), of the US Department of Health and Human Services.

DAWN provides semiannual estimates of the number of drug-related visits to hospital emergency departments based on a nationally representative sample (22 metropolitan areas) of short-stay general hospitals located throughout the US. In 2003, 122 jurisdictions in 35 metropolitan areas and 6 states submitted mortality data to DAWN, which is published annually. Endo will monitor these DAWN reports, when released, to identify geographic trends which may not be identified through standard post-marketing surveillance. The Agency will be notified if any area of increased activity for EN3202/03 is identified and Endo will initiate targeted education initiatives to the geographic region.

FDA's Freedom of Information. Endo has a licensing agreement with DrugLogic to view safety data on all pharmaceutical products, which are received by DrugLogic from FDA under the Freedom of Information Act. DrugLogic provides information regarding the number of adverse events received for other marketed products. EN3202/03 adverse event information that has been obtained via post marketing surveillance will be compared to other products of potential abuse, in this therapeutic class via FDA FOI data. Endo will use DrugLogic's Proportion Analysis Engine to look for deviations in reaction frequency for EN3202/03 compared to an expected value derived from a background set of drugs (e.g., comparing Oxycodone ER and/or morphine).

Media Screening. In addition to reviewing the medical literature on a continual basis, Endo has subscribed a media screening service which reviews the lay press for articles pertaining to opioid abuse, with specific searches regarding EN3202/03. This search will be performed regularly with a report generated at least monthly. If areas of increased media coverage regarding abuse or diversion of the product are identified, further investigation will be undertaken.

IMS Health Xponent database. The IMS prescribing database will be used in conjunction with the "aggregated" adverse event data to identify prescribing trends. The metrics used in this database include dispensed prescriptions with specialty physician details and ZIP code geographic detail. IMS captures the dispensed prescriptions from a robust sample of US retail pharmacies. The sample, taken on a monthly basis (with an approximate 1 month lag time), includes more than 30,000 of the approximately 55,000 US pharmacies (independent, chain, food store, mail order).

A number of databases have been developed to consolidate information pertaining to drug abuse and misuse in the U.S. Endo can draw on the information in these databases to help monitor the risks associated with OPANA™ and act on any problems they identify.

Primary and Secondary Prevention. Since a significant component of all prescription opioid abuse in this country is occurring in teens and young adults, working with Inflexxion, Endo will support two prevention programs designed to impact this population in a positive manner.

(1) *Mystudentbody: Drugs—MSB Drugs*. With NIH support, Inflexxion has developed and tested the country's largest and most extensive online suite of college health education programs, called *MyStudentBody (MSB)*. This suite of sites focuses on high risk areas for students such as Alcohol, STDs, Stress, Smoking, and Nutrition and so on. Endo's funding will allow Inflexxion to develop a new site to be called *MSB Drugs*.

MyStudentBody is currently being used by about 80 colleges and universities with a total student population of nearly 500,000. Subscribers are increasing by about 35% per year. College administrators and health personnel have indicated to Inflexxion that they would welcome an *MSB* component focused on prescription drug abuse. They view this issue as the next most important college based problem after binge drinking. In many schools concerns about prescription medications even exceed concerns about marijuana. The *MSB: Drug* site will feature components like 'rate yourself,' peer stories, prevention strategies, tailored information and an online course. Because the *MSB* suite (without the prescription drug site) is already being used so extensively around the country, it is likely that the addition of this new area would further increase the number of schools and students who are using *MyStudentBody*. This would further the

public health value of the program and teach students about problems associated with prescription opioid misuse. Other *MSB* sites have had major impacts on reducing high risk behaviors on campus and it is likely that *MSB Drugs* would have similar effectiveness.

(2) *Drugs4Real—D4R*. This online program is focused on preventing illicit and prescription drug abuse in high school students. *D4R* was developed and tested with NIDA support. This program would be distributed to high schools around the country. It is highly interactive and was developed and tested with input from high school students. *D4R* would be another opportunity to reach out to a large, at risk population and prevent prescription opioid abuse. Inflexxion has worked extensively with the high school population and developed a number of other preventive programs that are used widely around the country.

One of the best ways to avoid abuse of opioids is to teach children and young adults about the dangers. Information sites and interactive online programs have been developed to speak directly to teens and college students in the hopes that they will make informed decisions about opioids.

Quantitative Internet Surveillance Program (QISP). Many risk management programs include a program for monitoring the internet for mentions of specific prescription drugs in abuse-related contexts. Until recently none of these programs appeared to approach this issue in a systematic way. Endo has contracted with Inflexxion to support Inflexxion's Quantitative Internet Surveillance Program (QISP), which consists of routine monitoring of the rate of mentions of specific prescription opioid products on a group of selected abuse-related websites. Inflexxion has demonstrated that this innovative approach can track the mention rates and the rating of such mentions on Inflexxion's validated content rating system, and can distinguish mention rates of prescription opioids that are abused at different rates. The QISP will be used to monitor mentions of TRADEMARK as well as other relevant comparators for any apparent trends in abuse of the product among prescription opioid abusers.

Programs exist that can monitor mentions of a drug in online forums. Mentions of OPANA™ on certain forums can be tracked using these programs, and the information can be used to identify trends of abuse.

Summary

In addition to education, other tools will be utilized to minimize abuse and diversion of OPANA™. These include tamper-resistant prescription pads, oversight of the distribution chain, and extensive postmarketing surveillance.

Tamper-resistant prescription pads can help prevent forging and altering of written prescriptions, a common method of opioid diversion. Since all Schedule II drug prescriptions must be written, this is a powerful tool to reduce diversion.

Oversight of the distribution chain helps ensure that all of the drug reaches its destination. The DEA and law enforcement work closely with Endo in this vital endeavor.

A number of sources will be utilized for postmarketing surveillance of adverse events. These include spontaneous reports from physicians and patients, scientific literature, postmarketing clinical studies, and epidemiological studies. These can be collected from databases such as NAVIPPRO, TESS, DAWN, IMS Health Xponent, and QISP. The media can also be screened for articles on opioid abuse

Review Questions (III)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. Endo's periodic reports on postmarketing surveillance contain information on

   a. adverse events.
   b. opioid diversion.
   c. patient selection.
   d. prescriptions.

2. Which of the following risk management programs monitors internet mentions of drug abuse?

   a. DAWN
   b. NAVIPPRO
   c. QISP
   d. TESS

Check your responses on page __.

IV. Evaluation Plan

We have discussed the wealth of information that can be gathered from postmarketing surveillance, but information is useless without people to analyze it and take action. Endo has established teams of employees to review incoming data and develop intervention plans when abuse or misuse is discovered. These groups are the Endo Safety Review Board (ESRB) and the Risk Management Team.

Learning Objectives

1. State the role of the ESRB.
2. Identify scenarios in which Endo will take action to prevent abuse, misuse, and overdose of OPANA™.

Key Concepts

1. The role of the ESRB is to monitor in-house postmarketing data on adverse events. If they identify a problem or trend, they can address the issue by appropriate means.
2. Endo may take action if they discover diversion in the distribution chain; significant increases in misuse, abuse, dependence, overdose, or death in specific geographic regions; abnormally high prescribing areas; or localized areas of pharmacy theft.

A. Endo Safety Review Board

Endo has an established Safety Review Board (ESRB) to review adverse events and identify new safety signals and trends for all Endo products. The ESRB will review aggregate adverse event data received for EN3202/03 on a quarterly basis at a minimum. However, if Endo identifies a trend or signal prior to the quarterly review, the ESRB will address these issues promptly and independently.

The ESRB consists solely of Endo employees since it is an integral component of our internal safety surveillance process. It is a multi-disciplinary team with representatives from Scientific Affairs, Medical Affairs, Clinical Research & Development (as needed basis), Regulatory Affairs, Project Management, Pharmacovigilance and Risk Management (chair), and Pre-clinical Drug Safety (as needed basis). The ESRB will review adverse event data of EN3202/03 that have been collected as part of the post-marketing safety surveillance. As part of this surveillance, the ESRB will investigate and review all cases of clinical significance, misuse, abuse, dependence, overdose, death, and unexplained death to detect trends. Endo's review will include patient demographics, physician demographics and information about the use of concomitant medications when available. In addition, information obtained will be compared to other products of potential abuse in this therapeutic class. Once Endo has analyzed the information, if a trend is identified, the Agency will be notified and targeted education and safety measures will be initiated in the geographic area identified.

The ESRB is a board of Endo employees who will monitor all in-house postmarketing data and review significant cases. If any problems or trends are identified by their work, they are empowered to initiate education and safety measures to address the problem.

B. Risk Management Team

In addition to ESRB, a Risk Management Team has been formed at Endo which will meet on a monthly basis to evaluate data collected from post-marketing surveillance, secondary databases, media screening, and IMS data in order to assess risks of EN3202/03 while preserving its benefits. The team will be chaired by members of Pharmacovigilance and Risk Management Department with representations from Operations (supply chain), Regulatory Affairs, Clinical Development & Education, Market Research, Sales (as needed basis), Marketing department (as needed basis) and external consultants/advisors (as needed basis). The team will be responsible for longitudinal evaluation of all reports of misuse, abuse, dependence, overdose, death, and unexplained death received for EN3202/03 with the aim to identify trends and potential new safety signals, as well as develop and initiate targeted educational initiatives when warranted. These reports will be used in conjunction with IMS data for geographic trending in regards to the above events. Risk assessment will include data that represent a numerator, including cases of spontaneous reports of abuse, misuse, and addiction. The denominator would estimate patient exposure by using IMS data. Through these methods, a rough reporting rate can be calculated. In addition, to help identify trends, data also will be stratified by age, geographic region, and prescribing trends by specialty.

The team will be responsible for notifying the appropriate parties for intervention in the event a potential signal is identified. In addition, the Sponsor will send an analysis of all reports of misuse, abuse, dependence, overdose, death, and unexplained death received for EN3202/03 on a semiannual basis to the Agency.

The Risk Management Team is another board made up of Endo employees. This group is established to review and analyze all of the information collected from the programs described in earlier sections. As with the ESRB, when the Risk Management Team identifies a problem or trend, they will report it and begin the intervention process.

C. Risk Intervention

As per Endo's overall opioid RiskMAP, if Endo identifies any geographical areas of significant increases of abuse, misuse, or overdose with any of its opioids, including EN3202/03, Endo will take immediate and appropriate action, the specifics of which will depend upon the circumstances. Possible scenarios include:

- Diversion is suspected in distribution chain:
  - Endo will immediately alert the established security and management contacts at the manufacturing and distribution sites that may potentially be involved. These sites will investigate and search for possible diversion activities and will involve local DEA and law enforcement organizations as actionable details are discovered.
- Significant increase in cases of misuse, abuse, dependence, overdose, death, or unexplained death identified in specific geographic region by Risk Management Team:
  - Focused educational initiatives to targeted geographic area, which may be targeted towards health care providers, pharmacists, and/or the community
- IMS database identified high prescribing areas:
  - Refer to DEA for possible investigation unless internal investigation shows legitimate prescribing
- Localized area of local pharmacy thefts:

- Focused educational initiatives to targeted geographic area, which may be targeted towards health care providers, pharmacists, and/or the community.

Specific responses have been developed to react to any increases of abuse, misuse, or diversion in a specific geographical area. These plans call for focused responses to particular problems.

D. Endo Government Relations

Endo has a history of working closely with the FDA and DEA on many issues that relate to its marketed products and will continue such a relationship with regards to EN3202/03. Endo will also work closely with other government agencies and officials wherever appropriate to minimize diversion, misuse, and abuse of EN3202/03.

E. RiskMAP Semi-annual Report

Endo will submit a RiskMAP progress report to FDA on a semi-annual basis starting launch date presenting the evaluation results of this RiskMAP.

Summary

Endo has established the ESRB and the Risk Management Team for analysis of postmarketing data. The ESRB will review data on adverse events while the Risk Management Team will evaluate all postmarketing data to assess risks and preserve the benefits of OPANA™.

Endo may take action if they discover:

- diversion in the distribution chain
- significant increases in misuse, abuse, dependence, overdose, or death in specific geographic regions
- abnormally high prescribing areas
- localized areas of pharmacy theft

Review Questions (IV)

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. The role of the ESRB is to review all postmarketing data to identify possible problems.

   a. true
   b. false, its role is to review only adverse event data
   c. false, its role is to review only data on abuse

2. Which of the following responses would be appropriate if Endo discovered abnormally high prescribing of OPANA™ in a certain area?

   a. alerting the DEA to investigate

   b. alerting the sales representatives for the area to investigate suspicious prescribers

   c. focusing educational initiatives in that geographic area

   d. stopping all prescribing in that area until the cause is discovered

Check your responses on page __.

Integrative Summary

Opioids have been proven to increase functioning and quality of life in patients with chronic pain. However, opioid use carries risks including abuse and misuse, addiction, side effects such as respiratory depression, and diversion.

The AAPM and APS published a consensus statement in 1997 that proposed a plan to maximize proper use while minimizing the risks. Their plan involved publishing guidelines for opioid use, physician training, patient education, and monitoring to ensure that the plan is working correctly. Risk management plans based on this and other statements since have been developed for many opioids.

Opioid-related education programs should include information on many subjects, including careful selection of patients, patient assessment and reassessment, identification of patients at higher risk for abuse, appropriate documentation, actions for minimizing risk of abuse or accidental exposure, and differentiation among physical dependence, tolerance, and addiction. Many different types of education programs are available.

Education of sales representatives is especially important. Rigorous training in the concepts of risk management, laws governing representative relationships with providers, legal guidelines of the use of controlled substances and potential liability, and informing providers of additional resources are part of the RiskMAP.

In addition to education, other tools will be utilized to minimize abuse and diversion of OPANA™. These include tamper-resistant prescription pads, oversight of the distribution chain, and extensive postmarketing surveillance.

A number of sources will be used for postmarketing surveillance of adverse events. These include spontaneous reports from physicians or patients, the scientific literature, postmarketing clinical studies, and epidemiological studies. These can be collected from databases such

as NAVIPPRO, TESS, DAWN, IMS Health Xponent, and QISP. The media can also be screened for general articles on opioid abuse.

Endo has established the ESRB and the Risk Management Team to analyze postmarketing data. The ESRB will review data on adverse events, while the Risk Management Team will evaluate all postmarketing data to assess risks and preserve the benefits of OPANA™.

Answers to Review Questions

I. 1. b
2. d
3. d

II. 1. c
2. d
3. c

III. 1. a
2. c

IV. 1. b
2. a

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Self-assessment Post-test

DIRECTIONS. Circle the letter corresponding to the correct response in each of the following items.

1. The SOAPP was developed to help physicians

   a. assess chronic pain.
   b. choose appropriate patients for opioid therapy.
   c. determine whether a patient needs opioid therapy.
   d. keep track of his or her patients' past abuse problems.

2. Tamper-resistant prescription pads are particularly useful for Schedule II drugs because

   a. all prescriptions for Schedule II drugs must be written.

   b. they leave a paper trail for investigators to follow.

   c. they limit the amount of drug that may be dispensed with a single prescription.

   d. they require a code given only to accredited prescribers.

3. The goal of the AAPM/APS consensus statement was to

   a. prove opioids can improve quality of life.

   b. reduce the economic and social costs of pain.

   c. teach physicians to choose appropriate patients.

   d. urge government policies to focus on issues that lead to abuse and diversion.

4. Nearly half of prescription drug abuse is seen in people ages 12–25 years.

   a. true
   b. false, about 25% of abuse is by that age group
   c. false, about 75% of abuse is by that age group

5. The goals and objectives of the RiskMAP are to minimize all of the following problems with opioids, **except**

   a. children taking opioids.
   b. drug abuse, misuse, and addiction.
   c. improper patient selection.
   d. inadequate patient education.

6. Which of the following is a problem with many postmarketing databases?

   a. inadequate information
   b. inaccurate data
   c. inconsistent data
   d. out-of-date information

7. Which of the following is **not** available on the *pain.edu* website?

   a. downloadable pain management tools
   b. interactive case-based learning
   c. online continuing education credits
   d. patient education modules

8. The patient and family brochure "Understanding Your Pain: Taking Opioids Analgesics" provides patients with information on all of the following subjects, **except**

   a. how to avoid becoming addicted to opioids.
   b. how to take the medication.
   c. opioids' role in pain management.
   d. potential side effects.

9. *Painaction.com* is a website focusing on the _____.

   a. consumer
   b. pain specialist
   c. pharmacist
   d. physician

10. Endo will ensure that its sales representatives are adequately trained and communicating the proper messages to physicians through all of the following mechanisms, **except**

    a. market research on physician comprehension of messages.
    b. ride-alongs by district sales managers.
    c. tracking sales figures.
    d. written assessment after training.

11. Which of the following is **not** a feature of the NAVIPPRO system?

    a. data from an independent, scientifically based group
    b. interactive manipulation of data.
    c. product-specific medication data.
    d. real-time reporting of data.

12. One drawback of the DAWN system is that

    a. it cannot consolidate information by geographic area.
    b. it has no data from outside selected metropolitan areas.
    c. it only reports deaths, not serious side effects.
    d. the DEA does not accept its data as valid.

Check your responses on page __.

Answers to Self-assessment Post-test

1. b (page __, paragraph __)
2. a (page __, paragraph __)
3. d (page __, paragraph __)
4. a (page __, paragraph __)
5. a (page __, paragraph __)
6. d (page __, paragraph __)
7. d (page __, paragraph __)
8. a (page __, paragraph __)
9. a (page __, paragraph __)
10. c (page __, paragraph __)
11. b (page __, paragraph __)
12. b (page __, paragraph __)